RCE/1632/4

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REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

Address to:
Commissioner for Patents
Box RCE
Washington, DC 20231

Application Number	09/447,681
Filing Date	November 23, 1999
First Named Inventor	Roth, Jack
Art Unit	1632
Examiner Name	Crouch, Deborah
Attorney Docket Number	INRP:003--2

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114

a. ☐ Previously submitted
   i. ☐ Consider the amendment(s)/reply under 37 CFR 1.116 previously filed on _____
   (Any unentered amendment(s) referred to above will be entered).
   ii. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
   iii. ☐ Other _____

b. ☑ Enclosed
   i. ☑ Amendment/Reply
   ii. ☐ Affidavit(s)/Declaration(s)
   iii. ☐ Information Disclosure Statement (IDS)
   iv. ☐ Other _____

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2. Miscellaneous

a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

a. ☑ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 50-1212/INRP:003--2
   i. ☑ RCE fee required under 37 CFR 1.17(e)
   ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)
   iii. ☐ Other _____

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b. ☐ Check in the amount of $_____ enclosed

c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Name (Print/Type)	Gina N. Shishima	*Registration No. (Attorney/Agent)*	45,104
Signature		*Date*	July 28, 2003

CERTIFICATE OF MAILING OR TRANSMISSION

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July 28, 2003
Date

Gina N. Shishima

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Roth

Serial No.: 09/447,681

Filed: November 23, 1999

For: ADENOVIRUS p53 COMPOSITIONS AND METHODS

Group Art Unit: 1632

Examiner: Crouch, Deborah

Atty. Dkt. No.: INRP:003--2

RESPONSE TO FINAL OFFICE ACTION
DATED SEPTEMBER 27, 2002

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper is submitted in response to the Final Office Action dated September 27, 2002. Applicant is filing herewith his Request for Continued Examination (RCE), along with the required fee. Applicant filed a Notice of Appeal on December 27, 2002, which was received by the Patent Office on January 3, 2003. An Appeal Brief was filed on April 3, 2003 with a request and fee for a one-month extension of time. An Examiner's Answer was mailed on May 28, 2003. The deadline for filing this RCE is July 28, 2003, and thus, it is timely filed.

It is believed that no fee is due in connection with this response; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski L.L.P. Account No.: 50-1212/INRP:003--2.

Reconsideration of the application is respectfully requested.

RESPONSE TO OFFICE ACTION

A. Status of the Claims

Applicant filed a Notice of Appeal and Appeal Brief regarding the rejection of claims 67 and 86-89. An Examiner's Brief was mailed on May 28, 2003. Thus, claims 67 and 86-89 are the subject of this response. A copy of the pending claims is provided in Appendix A.

B. Claims Are Adequately Described

The Action rejects claims 67 and 86-89 as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Action argues that the claims contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Action at page 5. The Action also contends that the instant specification does not contemplate adenoviral vectors comprising a wild type p53 gene operably linked to a promoter or to a specific promoter. The Action admits there is "generic disclosure to other promoter/vector constructs" but contends that there is no specific disclosure of another vector construct. The Action then separately considers each passage from the Specification cited by the Applicant and concludes the passages fails "to provide written description for the claimed invention." It further alleges that at no place in the specification is the invention clearly set forth so that the reader would

realize what the Applicant perceived as his invention at the time of filing. Applicant respectfully traverses this rejection.

The written description requirement is whether the "description clearly allows persons of ordinary skill in the art to recognize that he or she invented what is claimed." MPEP 2163.02 (citing *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989)). Applicant contends that it is clear that the specification describes what is claimed in rejected claims 67, 86-89. The claims are generally directed to an "adenovirus vector comprising a wild type p53 gene under the control of a promoter." The written description of this application supports this claim and claims 67 and 87-89, which recite specific promoters. The specification makes clear that the inventor was in possession of the claimed invention:

- "In one specific embodiment, the invention concerns vector constructs for introducing wild type p53 genes (wt-*p53*) into affected target cells suspected of having mutant *p53* genes. These embodiments involve the preparation of a gene expression unit wherein the wt-*p53* gene is placed under the control of the β-actin promoter, and the unit is positioned in a reverse orientation into a retroviral vector." Specification at page 9, lines 6-12.

- In Example III, "The *p53* cDNA with its β-actin promoter was cloned into the LNSX retroviral vectors in ***both*** orientations." Specification at page 61, lines 29-30 (emphasis added).

- "While this affect [sic] was observed using the β-actin promoter and a retroviral expression vector, the inventors believe that this phenomenon ***will be applicable to other promoter/vector constructs for application in gene therapy***." Specification at page 8, line 25 to page 9, line 4 (emphasis added).

- "In addition to retroviruses, it is contemplated that ***other vectors can be employed, including adenovirus***...." Specification at page 14, lines 21-23 (emphasis added).

- "While the **β-actin promoter** is preferred, the invention is by no means limited to this promoter and one may also mention by way of example promoters derived from **RSV**, N2A, LN, LNSX, LNSN, **SV40**, LNCX or **CMV**." Specification at page 15, lines 1-4 (citations omitted) (emphasis added).

- "***Generally speaking***, such a promoter might include either a human cellular or viral promoter. While the β-actin promoter is preferred the invention is by no means limited to this promoter...." Specification at page 14, line 35-page 15, lines 2 (emphasis added).

- "While the retroviral construct aspect of the invention concerns the use of a β-actin promoter in reverse orientation, there is no limitation on the nature of the selected gene which one desires to have expressed. Thus, the invention concerns the use of antisense-encoding constructs ***as well as 'sense' constructs that encode a desired protein.***" Specification at page 16, lines 5-10.

Therefore, the Specification makes clear that 1) p53 sense constructs are contemplated in both orientations; 2) any discussion about antisense constructs applies to "sense" constructs such as p53; 3) constructs can be retroviral, but they may also be adenovirus constructs, and thus, are not limited to retroviruses; 4) promoters are discussed both generally and in the context of antisense constructs, in addition to CMV, RSV, and SV40 being specifically mentioned; and finally, 5) because an adenovirus can be used instead of retrovirus and since constructs are not limited to antisense constructs, applying equally to sense constructs, there is adequate written description for an "adenovirus vector comprising a wild type p53 gene under the control of a promoter," as well as for vectors with a CMV promoter.

In addition to the Declaration of Dr. Lou Zumstein, submitted with the Response filed on October 18, 2001, Applicant submitted the Declaration of Dr. Philip Hinds with the CPA filed on May 13, 2002. Both of these constitute evidence from a person of ordinary skill in the art to support the contention that the Applicant was in possession of the claimed invention at the time the priority application was filed. Applicant contends that the Action has not rebutted the evidence submitted by persons of ordinary skill in the art to maintain the rejection of these claims. Evidence, as opposed to examiner argument, should be required to meet the "preponderance of the evidence" standard set forth in MPEP § 2163.04. The declarations and

the identified portions of the specification show the written description requirement has been met. Accordingly, Applicant respectfully requests this rejection be withdrawn.

The Action contends that in the places where adenovirus or promoters claimed are disclosed, "each such disclosure is within the context of antisense RNA production." Office Action page 6. Applicant denies that adenoviruses are discussed in the application only in the context of antisense embodiments. The paragraph in which the Specification discloses that other vectors such as adenovirus can be used instead of a retrovirus begins, "In broader aspects of the invention, a preferred approach will involve the preparation of retroviral vectors which incorporate nucleic acid sequences encoding the desired construct, once introduced into the cell to be treated...." Specification at page 14, lines 9-12. The use of adenovirus is discusses in the context of "broader aspects of the invention," and retroviruses and antisense constructs are but examples of aspects of the invention. Similarly, as quoted above, the following paragraph discussing promoters indeed recites particular embodiments of the invention, such as antisense; however, it says, "***Generally speaking***, such a promoter might include either a human cellular or viral promoter. While the β-actin promoter is preferred the invention is by no means limited to this promoter...." Specification at page 14, line 35-page 15, lines 2 (emphasis added).

Because the Specification indicates to a skilled artisan that the inventor was in possession of the claimed invention at the time the application was filed, Applicant respectfully requests this rejection be withdrawn. Furthermore, because the application complies with 35 U.S.C. §112, the claims are entitled to the benefit of their priority date of October 13, 1992. 35 U.S.C. 120.

C. Claims 67 and 86 Are Not Anticipated under § 102 (b)

The Action rejects claims 67 and 86 as unpatentable over Liu *et al.* (1994) ("Liu") based on 35 U.S.C. § 102(b). It contends that Liu anticipates the claimed invention. Applicant respectfully traverse this rejection.

The present application claims priority to 07/960,513 ('513 application), filed October 13, 1992. Moreover, the Action levies a written description rejection based on the '513 application. Applicant once again asserts a claim of priority for the present application to the '513 application. As is discussed above, Applicant is entitled to a priority date of October 13, 1992.

Accordingly, claims 67 and 86 are not anticipated by Liu because it is not prior art against the claimed invention. Liu was published in 1994, while the present application is entitled to a priority date that precedes the Liu publication date. Because Liu is not prior art against the application, it cannot anticipate the claimed invention. Consequently, Applicant respectfully requests this rejection be withdrawn.

D. Claims 86-89 Are Not Obvious

The Final Office Action rejected claims 86-89 as obvious over the references of Chen *et al.* (1990) ("Chen reference") and Stratford-Perricaudet *et al.*. *Human Gene Therapy* 1, 241-256 (1990) ("Stratford-Perricaudet reference") in view of Wilkinson *et al.* (Wilkinson), Colicos *et al.* (Colicos), Rajan *et al.* (Rajan), and Hitt *et al.* (Hitt).

It alleges that the Chen reference teaches that wild-type p53 is expressed in transduced cells and that these cells fail to form tumors in nude mice. The Action also argues that the Stratford-Perricaudet reference teaches the correction of an enzyme deficiency related disorder in mice using an adenovirus comprising an ornithine transcarbamylase DNA sequence operably linked to the adenovirus major late promoter. The Action admits that neither the Chen or the Stratford-Perricaudet reference teaches an adenoviral vector comprising a wild-type p53 gene under the control of a promoter, but instead, relies upon Wilkinson as allegedly teaching an adenovirus expression system utilizing a CMV promoter to regulate expression of *lacZ*. The Action also contends that Colicos teaches an adenovirus vector containing the RSV promoter,

that Rajan teaches an adenoviral vector containing an SV40 promoter, and that Hitt teaches an adenovirus vector with a human actin promoter. The Action further argues that the motivation to make the claimed vectors is provided by the Chen reference's statement that expression of p53 in cells lacking functional p53 reverts the cells' transformed phenotype and suggests possible clinical use of p53 gene replacement. It also claims that further motivation is provided by the Stratford-Perricaudet reference, which allegedly states that adenoviral vectors can be used in human gene therapy procedures to restore impaired metabolism. Applicant respectfully traverses this rejection.

Three basic criteria must be met to establish a *prima facie* case of obviousness:

(1) "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings";
(2) "there must be a reasonable expectation of success"; and
(3) "the prior art reference (or references when combined) must teach or suggest all the claim limitations."
MPEP §2142.

In this case, there is no suggestion or motivation to combine references and there is no reasonable expectation of success, as will be discussed below. Accordingly, a proper *prima facie* case of obviousness has not been made. Furthermore, there are surprising and unexpected results regarding the claimed invention, as demonstrated by its success in clinical trials. Based on each of the reasons, Applicant respectfully request the rejection be withdrawn.

1. No motivation or suggestion to combine references

The Federal Circuit held in *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430 (Fed. Cir. 1990), that the mere fact that combination or modification of a reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the

desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. *See also* MPEP § 2143.01. Federal Circuit caselaw requires motivation ***to combine references.*** "To combine references (A) and (B) properly to reach the conclusion that the subject matter of a patent would have been obvious, case law requires that there must be some teaching, suggestion, or inference in either reference (A) or (B), or both, or knowledge generally available to one of ordinary skill in the relevant art that would lead one skilled in the art to combine the relevant teachings of references (A) and (B)." *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 U.S.P.Q. 657 (Fed. Cir. 1985). The Action has not satisfied the requirement that there be some motivation or suggestion to combine references. It provides neither the basis for combining the Chen reference with the Stratford-Perricaudet reference and the Wilkinson reference or the basis for combining the adenovirus vector of Stratford-Perricaudet or Wilkinson with the wt p53 gene of Chen. The Chen reference purportedly discloses a retroviral vector comprising a wild-type p53 gene sequence. The Action relies upon the Chen reference and the Stratford-Perricaudet reference to provide motivation to combine references.

The absence of a suggestion or motivation to combine is particularly true given both the absence of evidence in the Chen and Wilkinson references for using adenovirus in a therapeutic context and the limited success that the authors of the Stratford-Perricaudet reference reported when adenovirus was used.

As discussed in the Chen reference (*e.g.*, page 1579), retroviruses integrate into the genome, unlike adenoviruses. Thus, Chen mentions replacing mutated tumor suppressors with wild-type versions, which is possible in the context of retroviruses, but not adenoviruses. Chen reference at page 1579 ("These shared properties of RB and p53 reinforce the tumor suppressor

gene concept, including the possible clinical use of their ***replacement*** in appropriate tumor cells.") (Emphasis added.) There is no suggestion in any of the cited references that one should substitute the retroviral vector of Chen with the adenoviral vector Stratford-Perricaudet for the *p53* construct, any more than there is the suggestion to make the retroviral vector of Chen with the OTC gene of Stratford-Perricaudet.

As for the Stratford-Perricaudet reference, it involved providing the enzyme ornithine transcarbamylase (OTC) to hepatic cells in an adenoviral construct in which the OTC gene was under the control of the adenovirus major late promoter (MLP). The authors indicate that in one of two animals tested, long-term OTC expression was not observed. Page 252. Also, they found that "the OTC activity in some of the animals was not significantly altered." *Id.* A review of the data in that reference shows that only 4 of the 17 mice provided with the adenoviral OTC construct exhibited normal levels of OTC expression. *See* Table 1. The defect was only partially corrected in most of the mice and led to no physiological or phenotypic change. Relatively low levels of OTC production were seen in cells infected *in vitro*. *See* page 247. With this discouraging result, there is hardly motivation to use adenoviruses to transfer the p53 gene based on the Stratford-Perricaudet reference.

It should also be noted that because OTC is an enzyme, expression levels that are half that seen in normal cells are sufficient to achieve a normal phenotype. *See* page 252. Where p53 is involved, it has been suggested that overexpression is required for mediation of cell death. *See* Diller *et al.* (Appendix B). This makes the endeavor of producing an effective Ad-p53 construct potentially more difficult from a technical standpoint.

Moreover, other references in that time frame—Rosenfeld *et al.* 1991 (Appendix C), Rosenfeld *et al.*, 1992 (Appendix D), and Jaffe *et al.* (Appendix E)—reported poor results and

showed that the efficacy of adenovirus in a therapeutic context was sketchy. Attempts to use adenovirus to transfer the gene for cystic fibrosis transmembrane conductance (CFTR) into the pulmonary epithelium of cotton rats demonstrated gene transfer and expression of the CFTR protein in lung airway cells but showed no physiologic effect. Rosenfeld *et al.*, 1992. The reference of Rosenfeld *et al.*, 1991, is a *Science* article in which the authors showed lung expression of α1-antitrypsin protein but were also unable to show a physiologic effect. In fact, they estimated that the levels of expression they observed were only about 2% of the level required for protection of the lungs in humans, that is, at a level far below what is necessary for a physiologic effect.

The Jaffe *et al.* reference shows the introduction of the human α1-antitrypsin gene into the liver of normal rats by intraportal injection, where the gene was expressed and resulted in the secretion of the human protein into the plasma of the injected rats. However, the levels that were obtained were disappointingly not high enough to be of therapeutic value. Thus, where efforts were directed to the generation of vectors capable of producing biologically significant quantities of p53, use of the adenovirus was a questionable proposition at best. Therefore, the art at the time the application was filed indicates there was little, if any, motivation to use adenovirus as a vehicle for p53 and its use in a therapeutic context.

Other evidence as well supports the contention that there was no motivation to combine references to produce the claimed invention. As indicated in the specification of Application Serial No. 145826, which claims priority to the present application, in the early 1990s it was thought that p53 could not be incorporated into a packaging cell, such as those used to prepare adenovirus, as it would be toxic. E1B of adenovirus binds to p53, and this was thought to be another reason why adenovirus and p53 technology could not be combined.

Accordingly, there is no evidence that a person of ordinary skill in the art would have combined the expression of p53 from the Chen reference with the use of an adenovirus from the Stratford-Perricaudet.

Applicants note that "[i]t is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any on reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 U.S.P.Q. 416 (Fed. Cir. 1986).

Once again, Chen allegedly teaches a retrovirus vector with a wild-type *p53* gene under the control of an LTR promoter; Stratford-Perricaudet and Wilkinson allegedly teach an adenovirus vector with either an OTC gene under the control of the adenovirus major late promoter or a *lacZ* gene under the control of a CMV promoter, respectively. The references of Colicos, Rajan, and Hitt are cited respectively for the use of an adenoviral vector comprising an RSV promoter, the use of an adenovirus with an SV40 promoter, and the use of an adenovirus with a β-actin promoter. In each case the promoter drives the expression of a gene that is ***not*** a p53 gene and that is different from the other cited references. The Action merely points to references that disclose elements of the claimed invention and asserts it would have been obvious to the ordinary artisan at the time of the invention to use an adenoviral vector comprising a human wild-type *p53* gene operably linked to a specific promoter. Such an artisan would have to pick out *p53* as the gene to be expressed in an adenovirus vector and under the control of specific promoters. Applicant contends that the absence of a suggestion or motivation to combine renders any *prima facie* case of obviousness based on these references to be fatally flawed. There is nothing in Chen or Stratford-Perricaudet that suggests or motivates its combination with

each other or with any of Wilkinson, Colicos, Rajan, or Hitt to produce the claimed invention. Furthermore, the references of Wilkinson, Colicos, Rajan, and Hitt do not suggest that any of them be combined with Chen or Stratford-Perricaudet.

If anything, the references of Wilkinson, Colicos, Rajan, and Hitt teach away from the claimed invention because they fail to mention p53, and they discuss expression of other genes, none of which is a therapeutic gene. In fact, several of the genes were believe to contribute to transformation of cells. As the Action acknowledges, Wilkinson teaches the expression of ***lacZ***, not p53, under the control of a promoter. Similarly, Colicos teaches expressing the ***denV*** gene product, a DNA glycosylase from bacteriophage T4. Rajan discusses expression of **SV40 small-t antigen**, which is a viral protein from the SV40 virus. Finally, Hitt reports the expression of **E1A**, an adenovirus oncoprotein. At the time the application was filed, both E1A and small-t antigen were known to play roles in cell transformation—a process that is the opposite of tumor suppression. *See* Hitt at page 667 and Rajan at page 6557.

Even the Stratford-Perricaudet reference limits the use of adenovirus in a therapeutic setting by stating, "The metabolic changes in the mice, correlated with the presence of viral OTC transcripts over 1 year following the inoculation, demonstrate the feasibility of using adenovirus for direct *in vivo* transfer of an **enzyme-encoding gene.**" Stratford-Perricaudet at page 253 (emphasis added). p53 is not an enzyme-encoding gene. Furthermore, as discussed above, the very limited expression of the OTC gene in the context of adenovirus does not suggest or motivate the substitution of p53 for OTC as an effective treatment for cancer. None of the other cited references addresses this lack of therapeutic efficacy in a way that ultimately suggests or motivates that the cited references be combined to produce the claimed invention.

Patent law states, "The relevant portions of a reference include not only those teachings which would suggest particular aspects of an invention to one having ordinary skill in the art, but also those teachings which would lead such a person away from the claimed invention." *In re Mercier,* 185 U.S.P.Q. 774, 778 (C.C.P.A. 1975). The relevant portions of the references teach away from using adenoviruses to express p53. Thus, there is no suggestion to combine the teachings of Chen and Stratford-Perricaudet with any of the references of Wilkinson, Colicos, Rajan, and Hitt.

Moreover, because there is no mention of p53 in the context of five of the six of the cited references and no motivation or suggestion to combine any of them with the one reference that does—Chen—to produce the claimed invention, this combination of references does not render obvious the claimed invention. A proper *prima facie* case of obviousness has not been made. Therefore, this rejection should be withdrawn.

2. No likelihood of success

To render claims obvious, the relied upon references must also "reveal that in so making or carrying out, those of reasonable skill would have a reasonable expectation of success." *In re Vaeck*, 20 U.S.P.Q. 2d 1438, 1443 (Fed. Cir. 1991) *citing In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988).

In this case, the "expectation" issue here concerns what those of skill in the art would have predicted, *a priori*, regarding the ability of adenovirus to express p53, particularly in a therapeutic context as that is what the Examiner has relied upon as the basis for the motivation or suggestion to combine references. The Wilkinson, Colicos, Rajan, and Hitt are not relevant because they do not discuss the use of adenovirus in the context of a therapeutic gene. Moreover, the Stratford-Perricaudet reference, as well as the Rosenfeld *et al.* 1991, Rosenfeld *et al.*, 1992, and Jaffe *et al.* references, discussed above, makes it clear that what one of ordinary

skill in the art would have expected regarding the claimed invention was "very little." Expression results were generally poor, the efficacy of expression was low in a therapeutic context, and even the expression that was achieved in the cited reference of Stratford-Perricaudet can be distinguished based on the fact that OTC is an enzyme while p53 was thought to require overexpression. Thus, the evidence shows that a person of ordinary skill in the art would ***not*** expect to be successful. Consequently, the Action has not established another basis required for a proper *prima facie* case. This rejection should be withdrawn for the foregoing reason as well.

3. Obvious to try is an improper basis for a rejection

At best, the Action asserts an improper "obvious to try" grounds for rejection. *See Jones v. Hardy,* 220 USPQ 1021, 1026 (Fed. Cir. 1984). According to *In re Eli Lilly & Co.,* 14 USPQ2d 1741, 1743 (Fed. Cir. 1990), "[a]n 'obvious to try' situation exists when . . . further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result or indicate that the claimed result would be obtained if certain directions were pursued." The cited references fail to indicate that sufficient expression of p53 could be achieved in the context of an adenovirus vector and thus, qualify as promoting the attempt toward attaining the claimed invention, but nothing more.

Accordingly, Applicant contends that the vector claims are patentable over the cited references, and respectfully requests the withdrawal of this rejection for claims 86-89.

4. The claimed invention produced surprising and unexpected results

The claimed invention is directed to adenoviral vector compositions comprising p53 in the context of gene therapy. The PTO has widely espoused the view that gene therapy is an unpredictable area. For example, in an patent application related by priority to the present application (USN 08/459,713), Examiner David Guzo stated in an Office Action:

> The gene therapy art is **extremely unpredictable**. This unpredictability is manifested in the inability to achieve any clinically significant results in patients, the inability to regulate gene expression in transformed cells *in vivo*, the inability to maintain expression of the introduced gene in cells *in vivo* for significant periods, the inability to exclude tumorigenic effects from use of recombinant adenovirus vectors, the inability to even determine the biological activity of the gene therapy techniques, the inability to develop animal models which are predictive of the corresponding disease condition in humans, etc.

Response at page 4 (emphasis added) (Appendix F). Consequently, that any gene therapy is successful constitutes a surprising and unexpected result that could not have been predicted based on the prior art cited in this case. The prior art does not provide evidence of clinical efficacy and instead merely provides basic tools that the skilled artisan is expected to combine to create the claimed invention.

Applicant submits the Declaration of Deborah R. Wilson ("Declaration") (Appendix G) and its accompanying exhibits, which were previously filed in related application USN 08/459,713 and USN 09/413,109, as evidence that the claimed invention achieves the surprising and unexpected result of clinical efficacy. The Declaration states that Introgen Therapeutics, Inc., the assignee of the present application, has been "involved in a number of clinical trials for head and neck cancer, lung cancer, breast cancer, esophageal cancer, glioma, prostate cancer, advanced solid tumors, bladder cancer, and ovarian cancer" using its adenovirus-p53 composition (INGN 201, known as Introgen's Advexin® adenovirus p53 product). Declaration at ¶ 3. As of February 2002, INGN 201 was in phase III clinical trials for head an neck cancer, and phase II clinical trials were underway or completed for a number of other cancers. A total of 24 clinical trials were completed, in progress, or approved involving INGN 201 as of February 2002. Moreover, five additional clinical trials were completed or in progress involving another adenovirus-p53 composition from Schering-Plough as of the same date, and papers discussing

their safety and efficacy are included with the declaration. Finally, ten different NCI/CRADA studies involving INGN 201 have been completed, are underway, or will soon be initiated. Thus, there are **numerous** clinical trials and studies involving Ad-p53, indicating a therapeutic promise above and beyond its prospects 10 years ago when the priority application was filed.

Applicant also submits a number of scientific articles that show both the safety and efficacy of INGN 201 in clinical trials identified in the chart accompanying the Declaration, and also emphasize the surprising and unexpected results of Ad-p53 in the treatment of cancer.

When INGN 201 was administered to 28 non-small cell lung carcinoma (NSCLC) patients who had previously failed to respond to conventional therapies, two patients had a greater than 50% reduction in tumor size and in one patient, there was *no recurrence* of the tumor for *more than a year* after the treatment ended. Swisher *et al.*, 1999 (Appendix H). Equally significant was the observation that gene transfer appeared to be dose-dependent. *See* Swisher *et al.*, 2002 (Appendix I).

In another clinical trial with Ad-p53, four patients among 15 patients with advanced squamous cell carcinoma of the head and neck (SCCHN) were *free of disease* with a median follow-up time of 18.25 months after treat after surgery with INGN 201 treatment. Clayman *et al.*, 1999 (Appendix J).

In a phase II study with INGN 201 and radiation therapy, 12 of 19 patients, had no viable tumor three months after completion of therapy, that is, **63% of patients** demonstrated successful therapeutic results with the treatment. Swisher *et al.*, 2003 (Appendix K).

These clinical results are clearly unexpected and surprising over the state of the art at the time the priority application was filed, particularly over the references cited in the obviousness rejection. To this day, no gene therapy has been approved by the FDA for therapeutic

application. However, with a number of phase I and phase II Ad-p53 clinical trials completed or underway and ongoing phase III Ad-p53 clinical trials, Ad-p53 appears promising as one of the first, if not the first, such approved therapeutic.

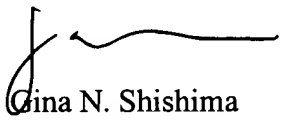
This evidence demonstrates the therapeutic value of adenovirus p53 compositions, which could not have been predicted based on the cited prior art. As such, this is additional evidence to rebut the contention that the claimed invention is obvious.

CONCLUSION

Applicant believes that the foregoing remarks fully respond to all outstanding matters for this application. Applicant respectfully requests that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3081 is respectfully requested.

Respectfully submitted,



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